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Markers of Recurrence and Long-Term Morbidity in Craniopharyngioma: A Systematic Analysis of 171 Patients

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Context: Craniopharyngiomas are often associated with an unfavorable prognosis, but data on their long-term consequences are sparse.

Objective: The aim of the study was to identify markers of recurrence and factors associated with compromised social rehabilitation and altered quality of life in a large cohort of patients with either childhood-onset (CO) or adult-onset craniopharyngioma.

Methods: Retrospective analysis was performed for 171 patients treated for craniopharyngioma in two academic centers in France between 1972 and 2009. For each subject, data were collected concerning clinical presentation, imaging features, visual sequelae, endocrine and metabolic impact, treatment modalities (surgery, radiotherapy), recurrence-free survival rate, and social insertion, as well as answers to the WHO-QOL BREF questionnaire.

Results: A total of 65 CO and 106 adult-onset patients were reviewed. If CO was diagnosed before the age of 10 yr, this was associated with a higher incidence of obesity, blindness, and panhypopituitarism, and only 40.7% of subjects had adequate work or school attendance compared to 72.4% of patients with later disease onset. Initial symptoms of intracranial hypertension (SIHT), pterional surgery, and multiple surgery were associated with obesity and poorer social insertion. No determinant of quality of life was identified. In the subgroup of patients treated in the 1990s and later, the progression rate was 59.4% in patients with residual tumor on magnetic resonance imaging compared with a 19.8% recurrence rate in the group with apparently complete resection. Recurrence/progression correlates significantly with male gender, early onset (before 10 yr), and SIHT, but only SIHT at presentation remained a significant predictor with multivariate analysis.

Conclusions: Craniopharyngioma continues to be associated with severe outcomes. Higher morbidity rates are found in patients with early-onset disease (before 10 yr), initial SIHT, or in whom pterional surgery was required. Markers of recurrence are difficult to identify, with SIHT being the most powerful predictor. **(*J Clin Endocrinol Metab* 97: 1258–1267, 2012)**

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Abbreviations: AO, Adult onset; BMI, body mass index; CO, childhood onset; MRI, magnetic resonance imaging; QoL, quality of life; SIHT, symptoms of intracranial hypertension.

Craniopharyngiomas account for 2–5% of all primary intracranial tumors (1). They can occur at any age but are more commonly diagnosed during childhood or adolescence (1, 2). They are histologically benign tumors, traditionally believed to arise from remnants of Rathke's pouch in the craniopharyngeal duct (3, 4). Despite their benign histological appearance, craniopharyngiomas are associated with increased mortality, as well as marked physical and cognitive sequelae adversely affecting quality of life (QoL) as a result of their proximity to the visual pathways, the pituitary gland, and the hypothalamus (2, 5).

Optimal treatment remains controversial. Gross total resection is associated with lower recurrence rates, but it carries a risk of damage to the visual pathways, the pituitary, or the hypothalamus (6–9). On the other hand, incomplete resection is associated with a high recurrence rate, further morbidity and mortality from tumor regrowth, as well as risk for repeated surgery. Another strategy is partial tumor removal supplemented by subsequent radiotherapy, either given as adjuvant therapy or at the time of relapse. Combined therapy may provide a better outcome and social rehabilitation score (10–13), despite concerns about potential adverse effects of irradiation, mainly risk of cognitive repercussions and radiation-induced secondary neoplasia (14, 15).

Because craniopharyngiomas are rare tumors and large cohorts are difficult to constitute, previous attempts to identify factors for prognosis or recurrence with a good correlation to long-term morbidity have failed to provide consistent markers. Moreover, adjuvant radiotherapy is frequently performed after partial tumor removal, making it difficult to collect data and conclusions about the natural history of the disease (12).

In the present study, we analyzed the clinical presentation, recurrence rate, long-term morbidity, and QoL in a large cohort of patients with childhood-onset (CO) and adult-onset (AO) craniopharyngiomas, followed over a long period to determine predictors of relapse, compromised social reinsertion, and impaired QoL.

Subjects and Methods

Study population

Retrospective analysis was performed of 171 cases of craniopharyngiomas treated at the endocrinology department of the Groupe Hospitalier de la Pitié-Salpêtrière-Paris and at the endocrinology and pediatric departments of the Centre Hospitalier de l'Université de Rennes. Subjects were identified from the general database of each department. Data were reviewed for all patients classified as being diagnosed with craniopharyngioma between 1972 and 2009. The diagnosis of craniopharyngioma was largely based on histopathological confirmation, but for three patients it was based upon characteristic features seen on neuroimaging.

Patients were separated into CO and AO craniopharyngiomas as is the standard practice. CO subjects were further stratified into two equivalent groups, aged either under 10 yr or between 10 and 18 yr at presentation, because younger CO subjects in the cohort appeared to present significant differences in terms of clinical presentation, recurrence rate, and long-term morbidity.

Analysis was performed for each group, and a comparison was made between CO and AO. For specific comparison of long-term morbidity and social insertion between CO and AO patients, the five CO patients aged under 18 yr at the last follow-up were excluded, enabling us to correlate comparable criteria, and thus limiting the cohort to 166 patients for final analysis of social rehabilitation.

Further analysis was also made for the subgroup of CO and AO diagnosed after 1990 (n = 123; 34 CO, 89 AO). The aim was to evaluate modern management of craniopharyngiomas and to validate certain risk factors for long-term morbidity since new surgical techniques and radiological evaluation by magnetic resonance imaging (MRI) was introduced in the 1990s. The specific impact of the presence of residual tumor was studied in this subgroup to limit bias resulting from more precise modern imaging techniques.

Clinical data and definitions

Residual tumor was defined as the presence of tumor reported by the radiologist based on the MRI or computed tomography scan obtained 3 to 6 months postoperatively. Diagnosis of recurrence was based upon detection of tumor or significant tumor growth on imaging more than 6 months after initial complete or partial surgical resection, with or without associated signs and symptoms. Time to recurrence was calculated from the date of initial surgery. Intracranial hypertension was diagnosed if severe hydrocephalus or symptoms of increased intracranial pressure were present.

At the time of medical assessment, pituitary functions were evaluated, and endocrine deficiencies were determined according to classic endocrine standards. Furthermore, almost all deficient patients received appropriate hormone replacement therapy. Panhypopituitarism was defined if three or more anterior pituitary deficits were present. A patient was considered epileptic if at least one seizure occurred and antiepileptic medication was prescribed. Blindness was defined as visual acuity of 1/10 or less

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in both eyes. Complete social rehabilitation was pronounced if subjects attended a regular school or worked in an institution without any program for persons with special needs or limitations. Inability to work was recorded if the patient was institutionalized or declared unfit for work (handicap ≥80% according to French social security standards).

QoL assessment was performed using the WHO-QOL BREF, a 26-item universally approved World Health Organization (WHO) QoL questionnaire that explores a subject's physical health (seven items), psychological health (six items), social relations (three items), and environment (eight items), with two final questions to assess the patient's perception of global QoL through individual scoring of overall appreciation of life and general sense of personal well-being. Answers to each question were coded from 1 to 5, summed, and placed on a scale from 0 to 100, with 100 representing the highest perception or level of QoL (16, 17). Surveys were sent by mail to all living patients, and answers were obtained from 97 patients (56.7% of the cohort).

Statistical analysis

All analyses were performed using SAS version 9.2 (SAS Institute, Cary, NC), and a two-sided level of $P < 0.05$ was considered statistically significant. Statistical calculations were based on the number of patients with data available for this evaluation. Comparisons of discrete variables were performed using a χ^2 test or Fisher's exact test, and continuous variables were compared using the Mann-Whitney *U* test. Survival and recurrence-free curves were generated using the Kaplan-Meier method, and differences in recurrence rates between the various subgroups were analyzed using Cox models. Analyses of recurrence were adjusted based on the presence of residual tumor. Logistic regressions were used to determine odds ratios for each outcome, with adjustment for follow-up, center (Rennes or Paris), and gender. Linear regression analysis was performed to determine the relationship between WHO-QOL BREF items and clinical presentation and management.

Results

Clinical presentation

Clinical features at presentation as reported in the medical files are displayed in Table 1. Mean age at presentation was respectively 5.5, 12.5, and 38.0 yr in each subgroup, with a range from 1.4 to 78.1 yr for the entire cohort. Almost two thirds of patients suffered from headaches, with similar figures for CO and AO patients. Visual acuity and/or field impairment were more frequent in patients with CO younger than 10 yr ($P < 0.01$). Intracranial hypertension was significantly more prevalent when craniopharyngioma was diagnosed before 10 yr, compared with CO 10–18 yr and AO patients. In contrast, hormonal-related symptoms were more common in the CO 10–18 yr subgroup and represent the most common presenting sign in this age group. Polyuria/polydipsia and proven central diabetes insipidus were reported in 13% of patients at presentation and were similarly distributed among the three age groups.

Tumor site and management

Only seven patients (4.09%) had a tumor localized to the pituitary not extending beyond the sellar margins (Table 1). Most patients with CO had both intra- and extrasellar craniopharyngiomas, and most craniopharyngiomas were smaller than 2 cm. On the other hand, adults had mostly extrasellar-only tumors and that were less than 2 cm. More CO patients had surgery performed before 1990, resulting in a shorter follow-up for AO craniopharyngiomas in our cohort. Most CO and AO patients had pterional surgery. The transphenoidal approach was used for only one CO patient younger than 10 yr, in 20% of CO patients 10–18 yr of age, and in 30% of adults. Radiotherapy was used significantly more often in CO than in AO patients. Radiotherapy was conventional fractionated external beam irradiation in almost all cases but two in which stereotactic radiosurgery was performed. Residual tumor based on imaging at 3 to 6 months was described in one third of patients.

Recurrences

In our cohort, the total recurrence rate, either recurrence after complete resection or progression after partial resection, was 35.7%, with 43.9% in the CO subgroup and 30.2% in adults. Moreover, in the subgroup of patients treated in the 1990s and later, the progression rate was 59.4% in patients with residual tumor compared with a 19.8% recurrence rate in the group with apparently complete resection (Fig. 1A). Most patients relapsed within 5 yr of initial surgery (median time to recurrence, 3.5 yr), although tumor recurred in one patient 19 yr after initial resection. Recurrence was more frequent in patients with CO younger than 10 yr (Fig. 1B), those with intracranial hypertension at presentation (Fig. 1C), and in male subjects (Fig. 1D). After adjustment for the presence of a residual tumor, male gender and intracranial hypertension remained significantly associated with a higher risk of recurrence. Recurrence was significantly more frequent in CO patients within 5 yr and remained significant after adjustment for the presence of a residual tumor ($P = 0.020$, data not shown). The relation between male gender and intracranial hypertension was no longer significant after further adjustment for intracranial hypertension. No difference was noted between recurrence-free survival rates according to tumor location (intrasellar, extrasellar, or both) or tumor size.

Long-term sequelae

Results for long-term sequelae for all adult patients are displayed in Table 2. Panhypopituitarism and diabetes insipidus were more frequent in CO than in AO craniopharyngiomas ($P < 0.01$). All patients with CO younger than

TABLE 1. Presentation and treatment approach according to age at presentation

	Aged under 10 yr at presentation (A) (n = 33)		Aged between 10 and 18 yr at presentation (B) (n = 32)		*P* value (A *vs.* B)	Aged above 18 yr at presentation (C) (n = 106)		*P* value (A + B *vs.* C)
	n[a]	n (%)	n[a]	n (%)		n[a]	n (%)	
Age (yr) at presentation, median (1st to 3rd quartiles)	32[b]	5.5 (4–6)	32	12.5 (11–15)		106	38 (28–52)	
Follow-up (months), median (1st to 3rd quartiles)	33	202 (166–280)	32	208 (24–343.5)	0.97	97	96.5 (36–167)	<0.01
Presenting clinical features								
Headaches	30	19 (63.3%)	31	18 (58.1%)	0.67	100	61 (61.0%)	0.97
SIHT	30	13 (43.3%)	28	6 (21.4%)	0.08	100	15 (15.0%)	<0.01
Polyuria/polydipsia and/or proven diabetes insipidus	29	4 (13.8%)	28	4 (14.3%)	1	100	12 (12.0%)	0.71
Any endocrine manifestation	33	16 (48.5%)	31	25 (80.6%)	<0.01	106	51 (48.1%)	0.04
Visual acuity and/or field impairment	28	23 (82.1%)	25	17 (68.0%)	0.23	101	72 (71.3%)	0.58
Location	32		29		0.21	105		<0.01
Intrasellar		1 (3.1%)		3 (10.3%)			3 (2.9%)	
Extrasellar		9 (28.1%)		8 (27.6%)			57 (54.3%)	
Both		24 (75.0%)		18 (62.1%)			45 (42.9%)	
Tumor size	20		18		0.04	73		0.19
<1 cm		0 (0.0%)		3 (16.7%)			11 (15.1%)	
1–2 cm		11 (55.0%)		12 (66.7%)			49 (67.1%)	
≥2 cm or described as large		9 (45.0%)		3 (16.7%)			13 (17.8%)	
Decade of surgery	32		32		0.97	104		<0.01
1970–1979		5 (15.6%)		4 (12.5%)			3 (2.8%)	
1980–1989		9 (28.1%)		8 (25.0%)			13 (12.3%)	
1990–1999		13 (40.6%)		15 (46.9%)			41 (38.7%)	
2000–2009		5 (15.6%)		5 (15.6%)			47 (45.2%)	
Residual tumor	31	11 (35.5%)	29	7 (24.1%)	0.34	103	33 (32.0%)	0.79
Surgical approach	30		30		0.10	105		0.01
Pterional		29 (96.7%)		24 (80.0%)			74 (70.5%)	
Transphenoidal		1 (3.3%)		6 (20.0%)			31 (29.5%)	
Radiotherapy	33	8 (24.2%)	30	9 (30.0%)	0.61	105	13 (12.4%)	0.02
Repeated surgery	33	4 (12.1%)	32	7 (21.9%)	0.34	106	6 (5.7%)	0.02

[a] Number of patients with available data for each item.

[b] Date of presentation is not known for one patient, but date of surgery is known.

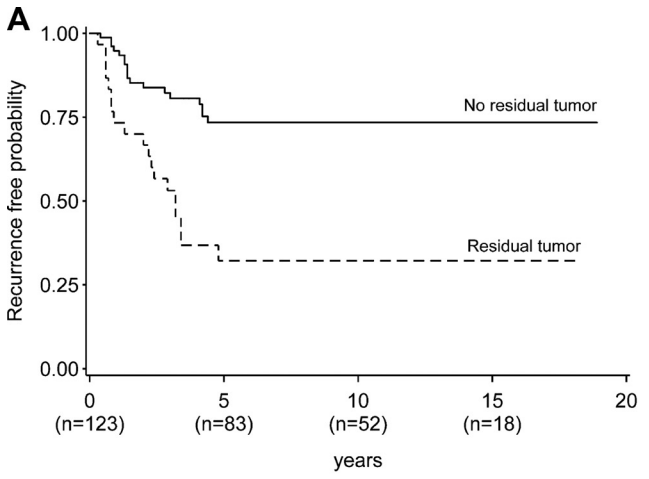
10 yr had at least three anterior pituitary deficits, and all but one had diabetes insipidus. In comparison, 73.8% of AO patients had at least three anterior pituitary deficits, and 68% had diabetes insipidus. The majority of patients with CO craniopharyngiomas (78.5%) had received GH supplementation during childhood. On the other hand, 37 patients had GH replacement during adulthood. Half of the cohort had major visual acuity and/or field impairment, with similar prevalence reported in all three age groups. However, total blindness was more often encountered in those with CO less than 10 yr of age.

CO patients less than 10 yr of age had a higher body mass index (BMI) at final evaluation and were more frequently obese compared with CO patients 10–18 yr old or AO patients (Table 2). Most of the weight gained was noted in the first year after diagnosis or surgery, and there was only a slight increase in BMI when comparing individual weight and BMI at 1 and 5 yr after surgery. Overall, long-term morbidity improved slightly after 1990, with particular improvement in CO patients less than 10 yr old, whereas the rate of blindness, epilepsy, and obesity fell (Supplemental Table 1, published on The Endocrine Society's Journals Online web site at http://jcem.endojournals.org).

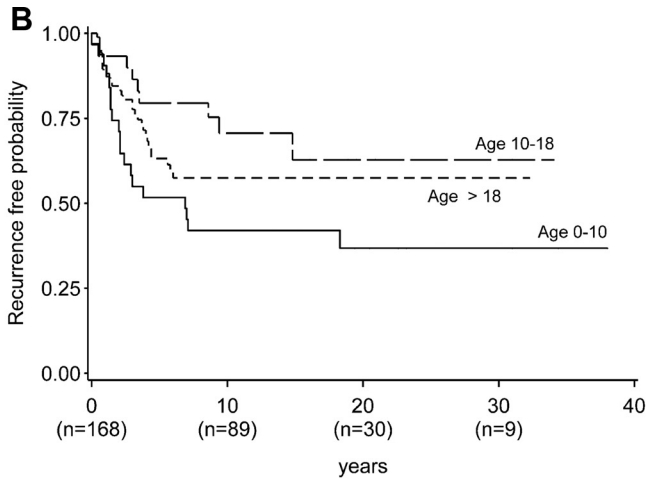
Functional outcome and QoL

Only 40.7% of CO patients younger than 10 yr had normal social insertion, rising to 53.8% when considering only patients diagnosed after 1990. Social integration was better in CO patients ages 10–18 yr and in AO patients, with complete social rehabilitation in 68.7 and 75.5%, respectively.

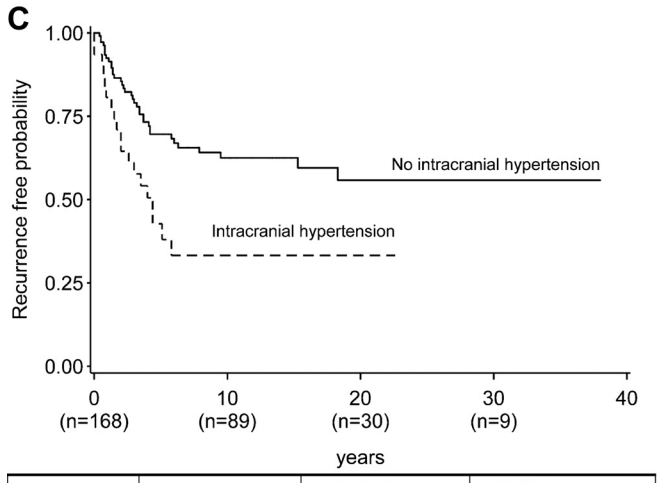
Scores for the physical health, psychological health, and social relationship components of the WHO-QOL BREF were lower in patients with craniopharyngiomas than in the general population (Table 3). Self-assessment of physical



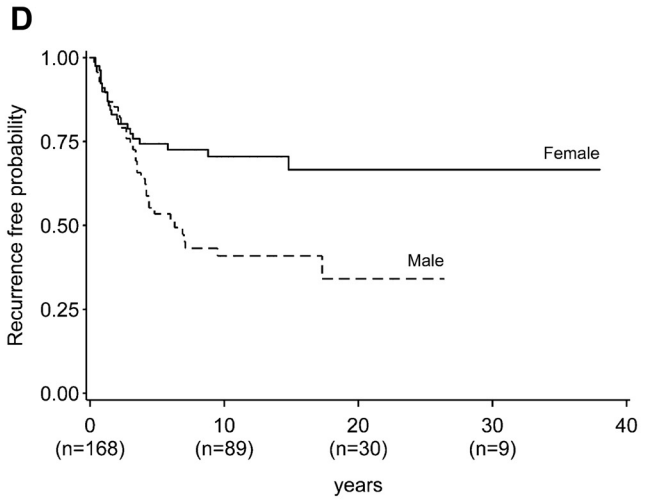
Univariate	HR (95%CI)	p-value
Residual tumor	3.43 (1.80 - 6.56)	<0.01



Age at presentation	Univariate		Residual tumor adjusted	
	HR (95%CI)	p-value	HR (95%CI)	p-value
< 10 yrs	1.00 (ref)		1.00 (ref)	
10-18 yrs	0.40 (0.18 0.88)	0.02	0.50 (0.22 1.12)	0.09
> 18 yrs	0.63 (0.35 1.13)	0.12	0.68 (0.38 1.23)	0.21



	Univariate		Residual tumor adjusted		Residual tumor and gender adjusted	
	HR (95%CI)	p-value	HR (95%CI)	p-value	HR (95%CI)	p-value
Symptoms of intracranial hypertension at presentation	2.12 (1.21 3.71)	<0.01	2.00 (1.14 3.52)	0.016	1.89 (1.07 3.34)	0.027



	Univariate		Residual tumor adjusted		Residual tumor and intracranial hypertension adjusted	
	HR (95%CI)	p-value	HR (95%CI)	p-value	HR (95%CI)	p-value
Male gender	2.02 (1.19 3.45)	0.009	1.79 (1.04 3.08)	0.036	1.59 (0.90 2.80)	0.108

FIG. 1. A, Recurrence-free probability according to the presence of a residual tumor on postoperative imaging in 127 patients with craniopharyngioma onset after 1990. B–D, Recurrence-free probability in CO (before 10 yr and 10–18 yr) and AO craniopharyngioma (B), in patients with or without intracranial hypertension at presentation (C), and in male and female patients (D).

health was 59.3%, compared with 76.9% in the general population and 64.4% in the French subpopulation with chronic disease. Self-assessment of psychological health was 53.5%, compared with 67.0% in the general population and 64.9% in the French subpopulation with chronic disease. Self-assessment of the social relationship item was 58.3%, compared with 74.5% in the general population and 71.5% in the French subpopulation with chronic disease. The reported QoL was similarly impaired in the three age groups of our cohort of craniopharyngioma patients. No risk factor for impaired QoL was identified (Table 4). Neither presentation characteristics nor tumor size, nor indeed therapeutic management were identified as predictive factors for poor QoL. Patients with no QoL data did not differ significantly in terms of age at presentation, gender, intracranial hypertension, pterional surgery, or recurrence rate.

Markers of long-term morbidity

Table 5 shows the odds ratios adjusted for gender, center, and duration of follow-up of various long-term morbidity outcomes associated with presenting clinical features and management. CO in patients younger than

TABLE 2. Prevalence (%) of various morbidities at final follow-up according to age at presentation in the 166 adults

Variables	Aged under 10 yr at presentation (A) (n = 28)		Aged between 10 and 18 yr at presentation (B) (n = 34)		*P* value (A *vs.* B)	Aged above 18 yr at presentation (C) (n = 104)		*P* value (A + B *vs.* C)
	n[a]	n (%)	n[a]	n (%)		n[a]	n (%)	
Endocrine sequelae								
At least three anterior pituitary insufficiencies	28	28 (100.0%)	34	28 (82.3%)	0.03	103	76 (73.8%)	0.01
Diabetes insipidus	28	27 (96.4%)	34	28 (82.3%)	0.12	103	70 (68.0%)	<0.01
Major visual acuity and field impairment	26	14 (53.8%)	34	17 (50.0%)	0.77	102	49 (48.0%)	0.66
Blindness	27	10 (37.0%)	34	2 (5.9%)	<0.01	103	14 (13.6%)	0.30
Epilepsy	28	9 (32.1%)	32	6 (18.7%)	0.23	103	16 (15.5%)	0.14
BMI (kg/m^2), median (1st–3rd quartiles)	28	33.1 (27.0–40.3)	33	26.2 (22.0–29.8)	<0.01	94	27.7 (25.0–33.1)	0.80
<25		5 (17.9%)		15 (45.4%)	<0.01		21 (22.3%)	0.16
25–30		4 (14.3%)		10 (30.3%)			34 (36.2%)	
>30		19 (67.9%)		8 (24.2%)			39 (41.5%)	
1-yr weight increase								
+1 SD or +3 kg/m^2	22	12 (54.6%)	24	11 (45.8%)	0.56	70	36 (51.4%)	0.88
+2 SD or +6 kg/m^2	22	9 (40.9%)	24	5 (20.8%)	0.14	70	13 (18.6%)	0.14
5-yr weight increase								
+1 SD or +3 kg/m^2	22	13 (59.1%)	24	14 (58.3%)	0.96	52	31 (59.6%)	0.93
+2 SD or +6 kg/m^2	22	9 (40.9%)	24	10 (41.7%)	0.96	52	16 (30.8%)	0.28

[a] Number of patients with available data for each item.

10 yr is associated with a higher morbidity rate: more blindness, partial or complete inability to work, and obesity, as well as a lower level of social insertion. Symptoms of intracranial hypertension (SIHT) at presentation are associated with a worse outcome, whereas an only hormonal-related manifestation is associated with a better outcome. Large tumors are associated with panhypopituitarism, and there is a trend toward increase blindness, inability to work, or obesity. Noticeably, the pejorative outcome of large tumors in terms of obesity and social insertion fell after 1990 to the same level as other tumors initially considered as large (Supplemental Table 2).

Pterional surgery was associated with a worse outcome than a transphenoidal approach in terms of panhypopituitarism, blindness, social insertion, and obesity (Table 5). Multiple surgery, the presence of a residual tumor, and radiotherapy (almost exclusively a second-line treatment option in our cohort) were associated with increased overall morbidity.

TABLE 3. Prevalence (%) of compromised social rehabilitation and impaired QoL assessed on WHO-QOL BREF at final follow-up visit according to age at presentation in the 166 adults

Variables	Aged under 10 yr at presentation (A) (n = 28)		Aged between 10 and 18 yr at presentation (B) (n = 34)		*P* value (A *vs.* B)	Aged above 18 yr at presentation (C) (n = 104)		*P* value (A + B *vs.* C)	French population with chronic disease[b]
	n[a]	n (%)	n[a]	n (%)		n[a]	n (%)		
Adequate social insertion	27	11 (40.7%)	32	22 (68.7%)	0.03	102	77 (75.49%)	0.01	
Inability to work	18	2 (11.1%)	21	1 (4.8%)	0.59	92	6 (6.52%)	1.00	
WHO-QOL BREF, median (quartiles)									
Physical health	17	60.7 (57.1–67.9)	21	64.3 (53.6–71.4)	0.67	59	57.1 (42.9–67.9)	0.21	64.4%
Psychological health	17	50.0 (45.8–54.2)	21	54.2 (41.7–62.5)	0.93	59	54.2 (41.7–62.5)	0.50	64.9%
Relationships	17	58.3 (41.7–91.7)	21	58.3 (41.7–75.0)	0.39	59	58.3 (50.0–66.7)	0.75	71.5%
Environment	17	68.7 (65.6–81.2)	21	65.6 (56.2–78.1)	0.51	59	68.7 (56.2–84.4)	0.92	

[a] Number of patients with available data for each item.

[b] Ref. 18.

TABLE 4. Associations between presentation characteristics, patient management, and the four QoL-related items on the WHO-QOL BREF score

Variables	Physical health (n = 97)		Psychological health (n = 97)		Relationships (n = 97)		Environment (n = 97)	
	β	*P* value	*β*	*P* value	*β*	*P* value	*β*	*P* value
Presentation characteristics								
Aged under 10 yr	−2.17	0.600	−3.99	0.308	7.26	0.305	−3.92	0.449
SIHT	−5.94	0.125	−4.35	0.228	−5.39	0.419	−3.02	0.533
Hormonal defect only at presentation	8.49	0.038	6.19	0.111	3.51	0.619	4.29	0.406
Tumor size ≥2 cm or described as large	1.94	0.700	−0.95	0.843	−1.89	0.832	−4.41	0.466
Management								
Pterional approach	−0.50	0.895	−4.54	0.192	−4.48	0.484	−1.89	0.683
Any recurrence	0.36	0.913	−1.31	0.676	−4.05	0.470	−1.05	0.799
Multiple surgeries	−2.39	0.658	0.73	0.886	1.22	0.895	−2.62	0.697
Radiotherapy	−2.68	0.534	1.16	0.773	−10.22	0.160	0.22	0.966

Linear regression-derived *β* coefficients and *P* values after adjustment for follow-up length, center (Rennes-Paris), and gender are presented.

Discussion

The present study showed in a large number of cases reinforcing data indicating that craniopharyngiomas remain associated with a severe outcome. In our cohort, higher morbidity was observed in patients with CO before 10 yr of age, initial SIHT, and in whom a pterional approach was required or performed. The characteristics of our cohort are similar to those for other previously published series of craniopharyngioma patients (2, 7, 8, 10–12). The large number of patients in our cohort allowed separate analysis and creation of subgroups according to age of onset, different patterns at clinical presentation, and decade of diagnosis. The majority of patients with CO younger than 10 yr had tumor-related symptoms at presentation. In particular, visual acuity and/or field impairment were more frequent in patients with CO younger than 10 yr, although the assessment of visual fields is difficult in young children and therefore is usually not performed before surgery. In contrast, endocrine-related symptoms were the main clinical presentation in patients with CO at 10–18 yr of age. Previous studies have suggested that SIHT were more frequent in younger children (18, 19); we show that a prevalence of SIHT in children is indeed observed for CO patients younger than 10 yr, but not for CO patients 10–18 yr old.

Few studies have been designed for specific identification of risk factors for specific long-term morbidity of craniopharyngioma. de Vile *et al.* (20) identified certain risk factors for increased morbidity: larger tumor size, hypothalamic involvement (mainly obesity), and diagnosis of craniopharyngioma before the age of 5 yr. A recent report found that preoperative functional impairment in 80 children with craniopharyngiomas was a better predictor of postoperative outcome than clinical characteristics such as age, sex, tumor size, tumor site, or presence of hydrocephalus (21). We also identified differences in long-term sequelae and social insertion according to various presenting features. SIHT at presentation is associated with a poor outcome, whereas only hormonal-related manifestations are associated with better recovery. A young age at presentation was also associated with increased morbidity, resulting in a high rate of partial or

TABLE 5. Risk of long-term morbidity and compromised functional outcome associated with presentation characteristics, tumor size, and medical management in the 166 adults

Variables	Panhypopituitarism	Blindness	Partial or complete inability to work	Normal social insertion	Weight increase ≥2 SD 1 yr after surgery	Obesity
Presentation						
Aged under 10 yr	NA	4.43 (1.52–12.90)	5.85 (0.43–80.20)	0.25 (0.10–0.64)	2.88 (0.97–8.58)	3.81 (1.51–9.62)
SIHT	1.70 (0.52–5.48)	2.02 (0.71–5.79)	2.30 (0.39–13.38)	0.32 (0.14–0.74)	4.11 (1.46–11.54)	3.17 (1.37–7.31)
Hormonal defect only at presentation	0.38 (0.14–1.03)	0.19 (0.024–1.529)	0.71 (0.07–7.03)	3.57 (0.98–13.00)	0.18 (0.02–1.47)	0.48 (0.17–1.34)
Tumor size ≥2 cm or described as large	9.20 (1.10–76.71)	4.00 (0.93–17.15)	4.23 (0.28–63.80)	0.58 (0.19–1.72)	1.51 (0.39–5.80)	1.83 (0.63–5.33)
Management						
Pterional approach	3.15 (1.30–7.67)	7.40 (0.94–58.41)	NA	0.17 (0.05–0.62)	6.42 (0.78–52.84)	6.15 (2.15–17.58)
Any recurrence	2.82 (0.96–8.25)	1.90 (0.70–5.21)	1.57 (0.20–12.17)	0.30 (0.14–0.67)	3.12 (1.11–8.71)	2.33 (1.10–4.92)
Multiple surgeries	3.33 (0.40–27.85)	1.72 (0.45–6.65)	NA	0.61 (0.20–1.89)	1.96 (0.50–7.58)	1.42 (0.47–4.26)
Radiotherapy	0.77 (0.26–2.30)	0.80 (0.24–2.70)	NA	0.88 (0.35–2.23)	4.04 (1.40–11.64)	1.79 (0.75–4.26)

Data are presented as follow-up length, center (Rennes-Paris), and gender-adjusted odds ratios (95% confidence interval). NA, Not applicable due to quasi-complete separation.

complete inability to work. This emphasizes the difficulty of management of craniopharyngiomas in younger children, characterized in this population by larger tumors and a high rate of intracranial hypertension, together with the consequence of early neurological damage on future development. A previous study comparing CO and AO craniopharyngiomas reported similar functional outcome in both groups, but comparison between CO patients was not performed (12). In our cohort, patients with CO less than 10 yr old had a similar follow-up to individuals with CO 10–18 yr old, whereas AO craniopharyngioma patients had shorter follow-up. Our results may therefore depict a falsely less severe picture of AO craniopharyngiomas. However, the median duration of follow-up in AO patients (8.5 yr) is longer than the median time of recurrence (3.5 yr), and the impact of a longer follow-up is thus probably not the sole and main explanation of the reduced social outcome in CO patients. Noticeably, long-term morbidity significantly improved after 1990 in patients with CO less than 10 yr old.

The management of recurrent tumors is difficult, and the optimal treatment modality remains a subject of debate (22). Previous studies reported low rates of total removal, increased perioperative mortality, and significantly lower Karnofsky Performance Status in patients undergoing repeated surgery (6–8, 12). Some authors therefore recommend the use of radiotherapy in situations of recurrence in the absence of immediate risk of optic nerve compression (11, 23). To address this issue, we compared long-term sequelae associated with either radiotherapy or multiple surgery. In the present cohort, radiotherapy is associated with a better outcome than multiple surgery, and this difference was more pronounced for patients with onset of craniopharyngioma after 1990. However, the numbers of patients undergoing multiple surgery (n = 45) or radiotherapy (n = 30) were low. Furthermore, the retrospective nature of the analysis impedes evaluation of management of recurrence because the choice of treatment reflects the location of the tumor, its intricacy, and the involvement of adjacent structures. Long-term evaluation of both strategies is needed, ideally through a randomized controlled trial.

Obesity is a major consequence of craniopharyngioma localization and treatment, and it was seen in 42.6% of patients in our cohort and in 26 to 80% in earlier studies (20, 24, 25). Damage to the hypothalamus, either preoperatively by the tumor or surgery-related, has been shown to be the main determinant of obesity, causing increased food intake through disruption of satiety and reduced energy expenditure (25–29). Visual impairment, somnolence, and vagally mediated hyperinsulinemia have all been described as contributory factors (29–31). We observed a very high rate of obesity in 67.9% of patients with CO less than 10 yr old, compared with 37% in the rest of the cohort. Other risk factors for later obesity are SIHT, pterional surgery, and recurrence, all of which were associated with hypothalamic lesion. Most of our patients had a normal BMI before surgery but developed rapid postoperative weight increase. More than half of the patients presented significant weight gain 1 yr after surgery. A dietary and physical activity program thus forms an essential part of craniopharyngioma management and should be implemented immediately after initial surgery in all subjects, including normal-weight patients with suspected hypothalamic involvement.

Reduced QoL has been reported in both CO and AO craniopharyngioma (2, 32–34). The largest study to date comes from the large Kabi International Metabolic Study database, a cohort treated with recombinant GH of a pharmaceutical company (2). This study showed that the score for the Quality of Life Assessment of GH Deficiency in Adults questionnaire was reduced in all patients and correlated with BMI and age at the onset of GH deficit. To our knowledge, this is the first study to evaluate QoL in a large sample of unselected patients with CO and AO craniopharyngiomas. In our cohort, all items on the WHO-QOL BREF questionnaire were reduced in comparison with a large sample of the French population with chronic diseases, thus confirming the generally poor state of health of these patients (18). However, items evaluated by the questionnaire did not significantly correlate with various clinical traits such as age, gender, tumor size, SIHT, and tumor management. In particular, QoL was similarly reduced in CO and AO patients. However, a self-questionnaire approach is limited for QoL assessment in patients with craniopharyngiomas because neurocognitive impairment induces misrepresentation and underreporting by patients, especially in those most severely impaired (35).

In our cohort, radiotherapy was not performed as adjuvant therapy after partial resection, but was performed almost exclusively as an alternative to further surgery on tumor recurrence. We are thus able to describe the natural progression of craniopharyngiomas before radiotherapy and determine risk factors for recurrence in a large subset of patients with onset after 1990 in whom MRI could be used to identify residual tumor. It has been reported that recurrence is frequent, even in the absence of an apparent residual tumor, usually occurring 2–5 yr after surgery (8, 12, 15, 36, 37). However, recurrence is still possible a long time after initial treatment, up to 19 yr in our cohort and up to 36 yr in a previous study (12), thus emphasizing the need for lifelong follow-up.

Risk of recurrence was associated with SIHT at presentation. This is consistent with earlier studies in small

cohorts stating that large lesions causing hydrocephalus may be associated with an increased recurrence rate (26, 38, 39). Large tumors causing intracranial hypertension are difficult to resect, and it has been suggested that the impact on recurrence may actually reflect incomplete resection (7). In our study, SIHT remained significantly associated with a higher risk of recurrence after adjustment for the presence of a residual tumor, as described by the radiologist on the imaging 3 to 6 months postoperative, pointing to the potential for growth of these aggressive tumors. These findings suggest the importance of close surveillance in patients with SIHT at presentation, regardless of the confirmation of residual tumor on postoperative imaging.

CO was not associated with risk of recurrence in previous studies, but one report in patients with childhood craniopharyngiomas showed that onset before the age of 5 was a significant predictor for recurrence (26). Considering the median age of 10 yr in CO patients in our cohort or the previously used cutoff age of 5 yr, we found a higher rate of recurrence in younger CO patients, although this was not significant after adjustment for the presence of a residual tumor. An increased recurrence rate in patients with onset at a young age is thus probably related to a higher rate of intracranial hypertension and the presence of a residual tumor.

No difference between genders in terms of recurrence was seen in two previous studies (1, 12). In the present study, male gender appeared to be a significant predictor of recurrence, even after adjustment for residual tumor. A higher prevalence of SIHT in male subjects probably accounts for this higher recurrence rate because the relationship between gender and recurrence disappeared after adjustment for SIHT.

Conclusions

Despite better outcomes in patients with disease onset after 1990, craniopharyngioma continues to be associated with severe sequelae and significant impairment of QoL and school/work status. Analysis of the published data shows that the growth rate of craniopharyngiomas varies considerably between individuals, and consistent markers predicting future relapse are lacking. Our study shows that onset before the age of 10 yr, SIHT at presentation, and the need for pterional surgery constitute independent risk factors for long-term morbidity and a poor prognosis. Recurrence is frequent, even where imaging 3–6 months postoperatively does not identify a residual tumor. SIHT appears to be the main predictor for later recurrence. In all cases, patients should undergo multidisciplinary therapy, including specialized care in neurosurgery, neuroimaging, endocrinology, nutrition, and neuropsychology.

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